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Original article

Variation of genes encoding KAT1, AADAT and IDO1 as a potential risk of depression development

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ABSTRACT

Numerous data suggests that the disorders of tryptophan catabolites (TRYCATs) pathway, including a decreased level of tryptophan or evaluated concentration of harmful TRYCATs –kynurenine, quinolinic acid, 3-hydroxyanthranilic acid, 3-hydroxytryptophan – may cause the occurrence of DD symptoms. In this work, we assessed the relationship between single-nucleotide polymorphisms (SNPs) of KAT1, KAT2 and IDO1 gene encoding, and the risk of depression development. Our study was performed on the DNA isolated from peripheral blood of 281 depressed patients and 236 controls. We genotyped, by using TaqMan probes, four polymorphisms: c.*456G > A of *KAT1* (rs10988134), c.975-7T > C of *AADAT* (rs1480544), c.-1849C > A (rs3824259) and c.-1493G > C(rs10089084)of *IDO1*. We found that only the A/A genotype of c.*456G > A – *KAT1* (rs10988134) increased the risk of depression occurrence. Interestingly, when we stratified the study group according to gender, this relationship was present only in male population. However, a gene–gene analysis revealed a link between the T/T-C/C genotype of c.975-7T > C – *AADAT* (rs1480544)or c.-1493G > C – *IDO1* (rs10089084) and C/C-C/A genotype of c.975-7T > C – *AADAT* (rs1480544)and c. –1849C > A – *IDO1* (rs3824259) and the disease. Moreover, we found, that the c.975-7T > C – *AADAT* and c. *456G > A *KAT1* (rs10988134) polymorphisms may modulate the effectiveness of selective serotonin reuptake inhibitors therapy. Concluding, our results confirm the hypothesis formulated in our recently published article that the SNPs of genes involved in TRYCATs pathway may modulate the risk of depression. This provides some further evidence that the pathway plays the crucial role in development of the disease.

1. Introduction

Depression (a depressive disorder, DD) is the most common mental disorder. All around the world, 300 million people suffer from DD [1]. Moreover, by 2020, depression will have become the second health and economic problem, second only to the ischemic heart disease [2]. Additionally, about 1/3 patients does not respond to the conventional therapy, and untreated or inappropriately treated depression may lead to suicide attempts [3]. Previous studies showed that the DD is regarded as multi-casual disease and its pathology remains unclear [4–7]. Additionally, depression is associated with numerous somatic disease – it increases the risk of developing the atherosclerotic heart disease, type 2 diabetes mellitus, cancer – and increases mortality rates [8–10]. Furthermore, recent studies showed, that DD occurrence is also strongly associated with obesity [11–14]. Interestingly, obese patients, similarly to depressed patients, were characterized by an imbalance of tryptophan catabolites (TRYCATs) pathway [15]. Our earlier study of single nucleotide polymorphisms (SNPs) of genes encoding tryptophan hydroxylase suggests that the tryptophan metabolism may play the key role in the pathophysiology of DD [16]. Another study showed that a decreased level of tryptophan or an elevated concentration of harmful TRYCATs, i.e. kynurenine, quinolinic acid, 3-hydroxyanthranilic acid, 3-hydroxytryptophan-may cause the DD symptoms to surface [6]. Although tryptophan is converted into toxic kynurenine, it also is a precursor of serotonin (5-HT) and melatonin – a main neurotransmitter that regulates the mood [17]. The first step of TRYCATs pathway, which is degradation

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of tryptophan to N-formylkynurenine, is catalysed by tryptophan 2,3-dioxygenase (TDO) or indoleamine-pyrrole-2,3-dioxygenase (IDO). There are rate-limiting enzymes of this pathway. TDO is expressed in liver and converts tryptophan only, whereas IDO is expressed in placenta, lungs, brain, blood – and, aside from tryptophan, it also metabolizes melatonin and serotonin [18,19]. Furthermore, the activity of IDO may be regulated by cytokines, whereas TDO does not depend on this regulation. Pro-inflammatory cytokines – interferon-γ (INFγ), interferon-α (INFα), and tumour necrosis factor-α (TNFα) – may act as potent activators of IDO. On the other hand, the anti-inflammatory cytokines may be inhibitors of the enzyme [20–22]. Clinical trials showed that the activity of IDO may be assessed by the examination of kynurenine/tryptophan ratio or by expression level of *IDO* [5,6]. The previous studies suggest that an increased activity of IDO and TDO may be an associated with occurrence of the depressive-like behaviours [23,24,5,6]. Moreover, an elevated kynurenine/tryptophan ratio may cause a development of anhedonia, which is the primary symptom of depression [25]. Animal studies confirmed that depression may be associated with an increased IDO expression/activity and levels of kynurenine, 5-hydroxykynurenine, quinolinic acid in brain areas, i.e. hippocampus, hypothalamus and amygdala [26–29]. Moreover, the IDO activation and serum level of the harmful TRYCATs were associated with the onset and severity of the disease symptoms [30–33]. Interestingly, the study showed that the female patients with the DD were characterized by a higher serum concentration of IDO, TNFα, INFγ but by a lower level of serotonin when compared to healthy volunteers. Moreover, the levels of IDO and TNFα were decreased in patients after antidepressant therapy [34,35]. In the same study, Zoga et al. [34] found a strong positive correlation between the concentration of IDO and INFγ. Moreover, transcription of *IDO1,* a gene encoding one of the protein isoform, is strongly controlled by cytokines. The gene promoter contains multiple sequence elements that induction of responsiveness to type I (INFα and –β) and type II (INFγ) interferons [36,37]. Induction of the expression by the latter one is mediated by a signal transducer and activator of transcription 1 (STAT1) and INF-regulatory factor 1 [38]. Moreover, IDO metabolizes the serotonin degradation into N-formyl-5-hydroxykynurenine; thus its over-expression results in a deficiency of the neurotransmitter [39]. Accordingly, the increased activity of the IDO and an impaired central serotonin system may lead to development of depression in patients with inflammatory disease [40,41]. The same study proved that glial cells secrete interleukin-6 (IL-6), interleukin-1 beta (IL-1β), TNF-α, and INF-γin response to injury and infection. Furthermore, it was found that DD could be potentially attributed to a hippocampal depletion of tryptophan, degradation of serotonin and increased level of kynurenine derived from serotonin degradation [6].

The next important step of TRYCATs pathway includes a conversion of kynurenine into kynurenic acid (enzyme – kynurenine formamidase) or, alternatively, into 3-hydroxykynurenine (3-HK), enzyme – kynurenine aminotransferase, up to date, its four isoforms have been described: KAT1/glutamine transaminase K (GTK)/cysteine conjugate beta-lyase (CCBL) 1, KAT2/aminoadipate aminotransferase (AADAT), KAT3/CCBL2 and KAT4/glutamicoxaloacetic transaminase (GOT) 2/mitochondrial aspartate aminotransferase (ASAT)or anthranilic acid (enzyme – kynurenine hydroxylase) [42]. Subsequently, 3-HK can be metabolized by kynureninase to form 3-hydroxyanthranilic acid (3-HAA), which can be further metabolized to form the quinolinic acid (QUIA) [43]. Although QUIA is neurotoxic, it cannot penetrate the blood-brain barrier. On the other hand, kynurenine is not neuroactive; however it may cross the blood-brain barrier and it generates free-radical-producing 3-HK or 3-HAA or is converted to the glutamatergically-active QUIA [43]. The harmful actions of TRYCATs may be related to an oxidative damage, inflammation, mitochondrial dysfunction, cytotoxicity, excitotoxicity, neurotoxicity and lowered neuroplasticity in central nervous system, e.g. 3-hydroxykynurenine may initiate neuronal apoptosis [44,45,6,7]. In contrast, some TRYCATs induce begin effects, e.g. kynurenic acid manifests antioxidant and neuroprotective properties which based on block N-methyl-D-aspartate (NMDA) receptors [44,45,5]. This acid is converted from kynurenine by kynurenineaminotransferase (KAT1 and KAT2/AADAT) Stone and Darlingtone, 2002. Therefore, the kynurenine/kynurenic acid (KYN/KA) ratio indicates a KAT activity (the ratio increase in inverse proportion to the KAT activity) and was found to be higher in depressed patients than controls [7]. Accordingly, an elevated expression of kynurenine aminotransferase in skeletal muscles can protect from depression [46]. Interestingly, the same study showed that physical exercise may be used as an alternative treatment of DD and that endurance exercise led to an increased expression of KAT in muscles, while the patients who were practising some sports/taking the training were characterized by an increased level of kynurenic acid in plasma. Another piece of evidence supporting involvement of TRYCATs pathway in depression development is the fact that abnormal activity of IDO may lead to impairment of serotonin metabolism and a decrease of melatonin level, and, in consequence, may trigger sleep disorders, all of these symptoms often present in the course of the disease [34]. Moreover, patients with depressive suicidal attempts suffer more frequently from severe insomnia than patents without the attempts [47].

The exact pathogenesis of the DD is unclear, genetic, environmental, and behavioral factors as well as interaction between them may be involved. Although the DD is recognized as a multifactorial disease, genetic factors may play the crucial role in its development, as was confirmed by segregation analyses, genetic epidemiological data and gene mapping studies. Several gene *loci*/chromosomal regions for DD have been mapped by genome-wide linkage analysis, including 12q23.3–q24.11 and 13q31.1–q31.3, 15q25.2 McGuffin et al., 2005, 3p21.1 Sullivian et al., 2013,19q12., 11p14.2, 8q22.2, 8q12.1, 8q23.3, 3p26.1, 2p25.1, 11p14.3, 6p22.3, 1q32.1, 3q26.1 (Shyn et al. 2011). These findings show a heterogeneous and complex genetic nature of the DD. Moreover, according to the study report, the genomic regions significantly associated with the DD were localized on chromosome 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14,15, 16, 17, 18, 22 Wray et al., 2017. Therefore, in this paper, we examine the link between single nucleotide polymorphisms (SNPs) of enzymes involved in TRYCATs pathway: c.*456G > A of *KAT1* (rs10988134, is located on 9q34.11), c.975-7T > C of *AADAT* (rs1480544, is located on 4q33), c.-1849C > A (rs3824259) and c.-1493G > C (rs10089084)of *IDO1* (is located on 8p11.21) and incidence of depression. Moreover, we detected differences between male or female groups in examined polymorphisms frequency. Interesting results were also obtained for the analysis an impact the single-nucleotide polymorphisms of genes encoding TRYCATs enzymes on effectiveness of antidepressant therapy.

2. Materials and methods

2.1. Subjects

281 patients with depression (age 49.53 ± 10.18, n male = 148, n female = 133) hospitalized at the Department of Adult Psychiatry of the Medical University of Lodz (Poland) and 236 healthy volunteers (age 53.19 ± 12.61, n male = 121, n female = 115) participated in the study. The Table 1. shows a detailed characteristic of depressed patients. All subjects in the control and depressed groups were native Poles from central Poland (not related), randomly selected without replacement sampling. All the participants had to meet

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Table 1
Detailed characteristic of patients taking part in the study.

Depression severity (HAMD range of scores)	Number of patients before treatment	Number of patients after treatment
None (0–7)	1	193
Mild (8–16)	35	85
Moderate (17–23)	94	3
Severe (≥24)	151	0
Mean age of patients with first episode		30
Mean age of patients with a further episode		50
Mean age of first episode (for all patients)		36
Duration of disease from the first episode		Number of patients
0-10 Years		147
11–20 Years		56
21–30 Years		50
31–40 years		26
≥41 years		2
Number of episodes		Number of patients
1		38
2		88
3		89
4		53
5		12
6		1

the inclusion criteria outlined in ICD-10 [48]. The axes I and II disorders, other than the DD, severe and chronic somatic diseases, injuries of the central nervous system, inflammatory or autoimmune disorders and unwillingness to give informed consent were exclusion criteria. Moreover, familial prevalence of mental disorders other than recurrent depressive disorders was also a factor of exclusion from the examined groups. Standardized Composite International Diagnostic Interview (CIDI) served as the guide to conducting a medical history for all cases before the study began. Evaluation and classification of depression severity were based on the Hamilton Depression Rating Scale (HDRS) [49]. The intensity of DD symptoms was measured in the study according to the grades proposed by Demyttenaere and De Fruyt [50] before and after antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI). The same psychiatrist examined each patient before the start of the study and after 8 weeks of pharmacotherapy. Participation in this study was voluntary. Its subjects were informed about the details of the study and assured of their voluntary participation in the experiment. Moreover, patients were guaranteed that their personal data would be kept secret before making a decision to participate in the study. During hospitalization, all the participants were treated according to antidepressant treatment standards. According to the protocol approved by the Bioethics Committee of the Medical University of Lodz (no. RNN/70/14/KE), all the subjects consented to participation in the study.

2.2. Selection of single nucleotide polymorphism

The public domain of the National Center for Biotechnology Information the Single Nucleotide Polymorphisms database (NCBI dbSNP) at http://www.ncbi.nlm.nih.gov/snp was used to identify potentially functional polymorphisms in genes encoding IDO and KAT. The four polymorphisms were chosen with a minor allele frequency (MAF) higher than 0.05 in the European population, respectively (submitter population ID: HapMap-CEU for both; http://www.ncbi.nlm.nih.gov/snp). The selection of studied polymorphisms was mainly determined by a potential biological significance – the localization of the SNPs was in the coding or regulatory regions of genes and might have functional meaning for transcription and protein function. The c.*456G > A(rs10988134) polymorphism of *KAT1* is localized in 3′ untranslated region and thec.975-7T > C (rs1480544) SNPis localized in intron of*AADAT*. The c.-1849C > A (rs3824259) and c.-1493G > C(rs10089084) polymorphisms are located near 5′ end of *IDO1*.

2.3. DNA extraction

We used the commercially available Blood Mini Kit (A&A Biotechnology, Gdynia, Poland) to extract genomic DNA from venous blood of patients with depression and from all controls. DNA purity and concentration were determined by measuring e absorbance at 260 and 280 nm. The sample of purified isolated DNA was stored at −20C until further analysis.

2.4. Genotyping

The TaqMans SNP Genotyping Assay (Thermo Fisher Scientific, Waltham, Massachusetts, USA) and 2X Master Mix Takyon for Probe Assay – No ROX (Eurogentec, Liège, Belgium) were used to genotype the studied SNPs in the Bio-Rad CFX96 Real-Time PCR Detection System and analysed in the CFX Manager Software (Bio-Rad Laboratories Inc., Hercules, California, USA). Theywere carried out the real-time polymerase chain reactions.

2.5. Statistical analysis

The SigmaPlot version 11.0 (Systat Software, Inc., San Jose, CA, USA), a statistical software package was used to the statistical analyses. The unconditional multiple logistic regression model was used to the evaluation of the correlation between case-control and each studied SNPs. This association was measured by the odds ratio (OR) with 95% confidence interval (95% CI). Additionally, the OR was adjusted for sex, since women have doubled risk of depression in comparison to men [51]. We also evaluated the correlation between the cases and controls for each studied polymorphisms in male/female population by used to unconditional logistic regression model. Distribution of genotypes according to the year of the first episode of depression and severity of actual depressed episodes are showed as the median ± inter-quartile range. The Shapiro-Wilks test was used to evaluate normality of the distribution. Next, the Mann-Whitney test or Student's *t* test was used to estimate the significance of the difference between the analysed values.

3. Results

3.1. Single nucleotide polymorphisms of the gene encoding TRYCATs enzymes (KAT1, AADAT, IDO1) as the risk of the depressive disorder

Table 2 shows the distribution of genotypes and alleles in patients with the DD and in controls, which is in agreement with the Hardy-Weinberg equilibrium. We only found that the A/A genotype of the c.*456G > A – *KAT1* (rs10988134) may increase the risk of depression occurrence. No correlation was found between depressed patients and healthy volunteers in terms of distribution of genotypes of the left-over studied polymorphisms.

3.2. Single-nucleotide polymorphisms of the genes encoding TRYCATs enzymes and the age of the first episode of depression, and the severity classification on the Hamilton Depression Rating Scale

No significant differences was found between distribution of genotypes and the severity classification on the Hamilton

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Table 2
Distribution of genotypes and alleles of c.*456G > A of *KAT1* (rs10988134), c.975-7T > C of*AADAT*(rs1480544), c.-1849C > A (rs3824259) and c.-1493G > C(rs10089084) of *IDO1* and incidence of depression.

Genotype/Allele	Control (n = 236)		Depression (n = 281)		Crude OR (95% CI)[a]	P	Adjusted OR (95% CI)[a]	P
	Number	Frequency	Number	Frequency				
c.[a]456G > A – *KAT1* (rs10988134)								
A/A	**9**	**0.038**	**23**	**0.082**	**2.266 (1.027–4.998)**	**0.043**	**2.269 (1.029–5.007)**	**0.042**
A/G	77	0.326	95	0.338	1.066 (0.738–1.540)	0.733	1.065 (0.737–1.539)	0.736
G/G	150	0.636	163	0.580	0.782 (0.548–1.117)	0.176	0.783 (0.548–1.117)	0.177
$\chi^2 = 3.659$; $p = 0.056$								
A	95	0.201	141	0.251	1.323 (0.991–1.766)	0.058	1.323 (0.991–1.766)	0.058
G	377	0.799	421	0.749	0.756 (0.566–1.009)	0.058	0.756 (0.566–1.009)	0.058
c.975-7T > C – *AADAT* (rs1480544)								
C/C	67	0.284	62	0.221	0.709 (0.475–1.059)	0.093	0.710 (0.475–1.060)	0.094
T/C	116	0.492	142	0.505	1.065 (0.753–1.506)	0.723	1.063 (0.751–1.504)	0.732
T/T	53	0.225	77	0.274	1.299 (0.868–1.945)	0.204	1.301 (0.869–1.949)	0.201
$\chi^2 = 3.283$; $p = 0.070$								
C	250	0.530	266	0.473	0.796 (0.622–1.020)	0.071	0.796 (0.622–1.019)	0.071
T	222	0.470	296	0.527	1.255 (0.981–1.607)	0.071	1.256 (0.981–1.607)	0.071
c.-1849C > A – *IDO1* (rs3824259)								
C/C	53	0.225	79	0.281	1.340 (0.896–2.003)	0.154	1.336 (0.893–1.999)	0.158
C/A	115	0.487	131	0.466	0.918 (0.649–1.299)	0.629	0.920 (0.650–1.303)	0.640
A/A	68	0.288	71	0.253	0.843 (0.571–1.245)	0.392	0.843 (0.571–1.245)	0.390
$\chi^2 = 1.920$; $p = 0.166$								
C	221	0.468	289	0.514	1.185 (0.932–1.507)	0.167	1.184 (0.931–1.506)	0.169
A	251	0.532	273	0.486	0.844 (0.664–1.073)	0.167	0.845 (0.664–1.074)	0.169
c. −1493G > C – *IDO1* (rs10089084)								
G/G	39	0.165	46	0.164	0.997 (0.625–1.591)	0.991	0.996 (0.624–1.589)	0.986
G/C	125	0.530	136	0.484	0.833 (0.588–1.178)	0.301	0.833 (0.589–1.179)	0.303
C/C	72	0.305	99	0.352	1.233 (0.852–1.786)	0.267	1.233 (0.851–1.786)	0.268
$\chi^2 = 0.592$; $p = 0.442$								
G	203	0.430	228	0.406	0.905 (0.703–1.167)	0.442	0.905 (0.702–1.166)	0.440
C	269	0.570	334	0.594	1.105 (0.857–1.423)	0.442	1.105 (0.857–1.424)	0.440

$p<0.05$ along with corresponding Ors are in bold.
[a] OR adjusted for sex.

Depression Rating Scale. Neither did we observe the defferences in the distribution of genotypes and the age distribution of the first depressive episode (Supplementary Fig. 1 and Supplementary Fig. 2).

3.3. Gene-gene interactions and the risk of depression

Gene-gene interactions as a risk of depressive disorder is showed in Table 3. We observed that the T/T-C/C combined genotype of the c.975-71T > C – *AADAT* (rs1480544) and the c.-1493G > C – *IDO1* (rs10089084) more than doubled the risk of the DD occurrence, while the C/C-C/A genotype of the c.975-7T > C – *AADAT* (rs1480544) and the c. C > A – *IDO1*(rs3824259) polymorphism combination reduced this risk. No statistical correlation was found between the combined genotypes of c. *456G > A (rs10988134) – *KAT1* and c.-1849C > A – *IDO1* (rs3824259), c.*456G > A (rs10988134) – *KAT1* and – *IDO1* (rs10089084), c.975-7T > C – *AADAT*(rs1480544) and c.*456G > A – *KAT1* (rs10988134) and development of depression.

3.4. Haplotypes and the risk of occurrence of depression

We also analysed if the haplotypes of the studied polymorphisms is associated with occurrence of depression and the results are presented in Table 4. We found that the CC haplotype of the c.-1849C > A – *IDO1* (rs3824259) and c.-1493G > C – *IDO1* (rs10089084) polymorphism increased the risk of depression occurrence. However, we did not observe a connection between depression and other haplotypes of the studied polymorphisms of*IDO1*gene.

3.5. Single-nucleotide polymorphisms of genes encoding enzymes of TRYCATs pathway depression occurrence in male and female population

Kessler [51] observed that women were exposed to a doubled risk of depression when compared to men. Therefore, we studied the connection between the depression occurrence in male or female groups and all examined polymorphisms (Table 5). On the one hand, we found that the A/A genotype and A allele of the c. *456G > A – *KAT1* (rs10988134) were association with an increased risk of depression development in male population, while in female population we did not observe this correlation. On the other hand, the G/G genotype and the G allele of the same polymorphism were linked to a lower risk in male population, while this dependence was not observed in females. Moreover, we investigated the relationship between the distribution of genotypes or alleles and gender in patients with depression but this association was not found for all the studied polymorphisms (data not published).

3.6. Single-nucleotide polymorphisms of genes encoding TRYCATs enzymes of and effectiveness of treatmentof the depression

We also study an impact the single-nucleotide polymorphisms of genes encoding TRYCATs enzymes on the effectiveness of

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Table 3
Gene-gene interactions of studied polymorphisms and the risk of DD.

Combined genotype	Control (n = 236)		Depression (n = 281)		Crude OR (95% CI)[a]	p	Adjusted OR (95% CI)[a]	p
	Number	Frequency	Number	Frequency				
c.[a]456G > A (rs10988134) – *KAT1* and c. –1849C > A – *IDO1* (rs3824259)								
A/A-C/C	1	0.004	7	0.025	6.004 (0.733–49.151)	0.095	5.953 (0.726–48.807)	0.097
A/A–C/A	3	0.013	11	0.039	3.164 (0.872–11.478)	0.080	3.185 (0.877–11,561)	0.078
A/A-A/A	5	0.021	5	0.18	0.837 (0.239–2.927)	0.781	0.843 (0.241–2.949)	0.789
G/A-C/C	13	0.055	28	0.100	1.898 (0.960–3.755)	0.065	1.890 (0.955–3.744)	0.068
G/A-C/A	40	0.169	44	0.157	0.910 (0.570–1.453)	0.692	0.911 (0.570–1.455)	0.696
G/A-A/A	24	0.101	23	0.082	0.787 (0.432–1.435)	0.435	0.789 (0.433–1.438)	0.439
G/G-C/C	39	0.165	44	0.157	0.938 (0.586–1.501)	0.789	0.939 (0.586–1.503)	0.792
G/G-C/A	72	0.305	76	0.270	0.844 (0.576–1.238)	0.386	0.846 (0.577–1.240)	0.390
G/G-A/A	39	0.165	43	0.153	0.913 (0.569–1.464)	0.705	0.910 (0.567–1.461)	0.696
c.[a]456G > A (rs10988134) – *KAT1* and c. –1493G > C – *IDO1* (rs10089084)								
G/G-G/G	1	0.004	5	0.018	4.257 (0.494–36.697)	0.187	4.205 (0.486–36.349)	0.192
G/G-G/C	6	0.025	10	0.036	1.415 (0.506–3.951)	0.498	1.428 (0.510–3.995)	0.497
G/G-C/C	2	0.008	8	0.028	3.429 (0.721–16.304)	0.121	3.433 (0.722–16.330)	0.121
G/A-G/G	11	0.047	17	0.060	1.317 (0.604–2.870)	0.488	1.319 (0.605–2.874)	0.486
G/A-G/C	39	0.165	46	0.164	0.989 (0.620–1.577)	0.962	0.987 (0.618–1.574)	0.955
G/A-C/C	27	0.114	32	0.114	0.995 (0.577–1.714)	0.985	0.996 (0.578–1.716)	0.987
A/A-G/G	27	0.114	24	0.085	0.723 (0.405–1.290)	0.272	0.722 (0.405–1.290)	0.271
A/A-G/C	80	0.339	80	0.285	0.776 (0.534–1.128)	0.184	0.777 (0.535–1.129)	0.186
A/A-C/C	43	0.182	59	0.210	1.193 (0.770–1.848)	0.430	1.192 (0.769–1.847)	0.431
c.975-7T > C – *AADAT* (rs1480544) and c. –1493G > C – *IDO1* (rs10089084)								
C/C-G/G	10	0.042	9	0.032	0.748 (0.299–1.872)	0.535	0.742 (0.296–1.861)	0.525
C/C-G/C	39	0.165	30	0.107	0.604 (0.362–1.007)	0.053	0.606 (0.363–1.012)	0.055
C/C-C/C	18	0.076	23	0.082	1.080 (0.568–2.053)	0.815	1.076 (0.565–2.046)	0.824
T/C-G/G	19	0.081	27	0.096	1.214 (0.657–2.244)	0.536	1.219 (0.659–2.255)	0.527
T/C-G/C	56	0.237	68	0.242	1.026 (0.684–1.539)	0.901	1.021 (0.679–1.533)	0.922
T/C-C/C	41	0.174	47	0.167	0.955 (0.603–1.513)	0.845	0.957 (0.604–1.515)	0.850
T/T-G/G	10	0.042	10	0.036	0.834 (0.341–2.039)	0.691	0.827 (0.338–2.025)	0.678
T/T-G/C	30	0.127	38	0.135	1.074 (0.643–1.794)	0.786	1.078 (0.645–1.803)	0.773
T/T-C/C	**13**	**0.055**	**29**	**0.103**	**1.974 (1.002–3.891)**	**0.049**	**1.977 (1.003–3.897)**	**0.049**
c.975-7T > C – *AADAT* (rs1480544) and c.*456G > A – *KAT1* (rs10988134)								
C/C-A/A	2	0.008	6	0.021	2.553 (0.510–12.768)	0.254	2.527 (0.504–12.664)	0.260
C/C-G/A	24	0.102	19	0.068	0.641 (0.342–1.201)	0.165	0.640 (0.341–1.200)	0.164
C/C-G/G	41	0.174	37	0.132	0.721 (0.445–1.169)	0.184	0.723 (0.446–1.173)	0.189
T/C-A/A	5	0.021	7	0.025	1.180 (0.370–3.768)	0.780	1.194 (0.373–3.819)	0.765
T/C-G/A	32	0.136	56	0.199	1.587 (0.988–2.548)	0.056	1.584 (0.986–2.545)	0.057
T/C-G/G	79	0.335	79	0.281	0.777 (0.534–1.131)	0.188	0.775 (0.532–1.128)	0.183
T/T-A/A	2	0.008	10	0.036	4.317 (0.937–19.903)	0.061	4.324 (0.938–19.935)	0.060
T/T-G/A	21	0.089	20	0.071	0.785 (0.414–1.485)	0.456	0.786 (0.415–1.488)	0.460
T/T-G/G	30	0.127	47	0.167	1.379 (0.841–2.262)	0.203	1.381 (0.842–2.265)	0.202
c.975-7T > C – *AADAT* (rs1480544) and c. –1849C > A – *IDO1* (rs3824259)								
C/C-C/C	12	0.051	20	0.071	1.430 (0.684–2.991)	0.342	1.423 (0.680–2.978)	0.349
C/C-C/A	**40**	**0.169**	**26**	**0.093**	**0.500 (0.295–0.847)**	**0.010**	**0.501 (0.295–0.850)**	**0.010**
C/C-A/A	15	0.064	16	0.057	0.890 (0.430–1.840)	0.752	0.886 (0.428–1.834)	0.745
T/C-C/C	29	0.123	40	0.142	1.185 (0.709–1.978)	0.517	1.181 (0.707–1.973)	0.526
T/C-C/A	53	0.225	63	0.224	0.998 (0.659–1.511)	0.992	0.997 (0.658–1.509)	0.988
T/C-A/A	34	0.144	39	0.139	0.957 (0.583–1.573)	0.864	0.958 (0.583–1.574)	0.866
T/T-C/C	12	0.051	19	0.068	1.354 (0.643–2.850)	0.425	1.360 (0.646–2.864)	0.419
T/T-C/A	22	0.093	42	0.149	1.709 (0.988–2.956)	0.055	1.710 (0989–2.958)	0.055
T/T-A/A	19	0.081	16	0.057	0.690 (0.346–1.373)	0.290	0.690 (0.346–1.374)	0.291

$p < 0.05$ along with corresponding Ors are in bold.
[a] OR adjusted for sex.

Table 4
Haplotypes of *IDO1* and the risk of depression.

Haplotype	Control (n = 236)		Depression (n = 281)		Crude OR (95% CI)	p
	Number	Frequency	Number	Frequency		
c.-1849C > A – *IDO1* (rs3824259) and c. –1493G > C – *IDO1* (rs10089084)						
CG	132	0.14	158	0.14	1.006 (0.784–1.291)	0.967
CC	**310**	**0.33**	**420**	**0.37**	**1.215 (1.013–1.457)**	**0.036**
AG	274	0.29	298	0.27	0.882 (0.727–1.070)	0.203
AC	228	0.24	248	0.22	0.889 (0.724–1.092)	0.261

$p < 0.05$ along with corresponding ORs are in bold.

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Table 5
Distribution of genotypes and alleles of the c.*456G > A of *KAT1* (rs10988134), c.975-7T > C of*AADAT*(rs1480544), c.-1849C > A (rs3824259) and c.-1493G > C (rs10089084) of *IDO1* and the risk of DD in male and female population.

Genotype/Allele	MEN (n = 169)				WOMEN (n = 248)			
	Control (n = 121)	Depression (n = 148)	Crude OR (95% CI)*	p	Control (n = 115)	Depression (n = 133)	Crude OR (95% CI)*	p
	N (Freq.)	N (Freq.)			N (Freq.)	N (Freq.)		
c.*456G > A – *KAT1* (rs10988134)								
A/A	3 (0.025)	**13 (0.088)**	**3.816 (1.061–13.718)**	**0.040**	6 (0.052)	10 (0.075)	1.489 (0.524–4.232)	0.455
A/G	37 (0.306)	54 (0.365)	1.318 (0.790–2.199)	0.290	40 (0.348)	41 (0.308)	0.845 (0.496–1.438)	0.534
G/G	**81 (0.669)**	**81 (0.547)**	**0.590 (0.358–0.971)**	**0.038**	69 (0.600)	82 (0.617)	1.059 (0.635–1.766)	0.827
$\chi^2 = 5.228$; $p = 0.022$						$\chi^2 = 0.386$; $p = 0.534$		
A	**43 (0.178)**	**80 (0.270)**	**1.705 (1.124–2.589)**	**0.012**	52 (0.226)	48 (0.180)	1.027 (0.683–1.542)	0.899
G	**199 (0.822)**	**216 (0.730)**	**0.586 (0.386–0.890)**	**0.012**	178 (0.774)	182 (0.684)	0.974 (0.648–1.463)	0.899
c.975-7T > C – *AADAT* (rs1480544)								
C/C	33 (0.273)	32 (0.216)	0.742 (0.424–1.299)	0.296	34 (0.296)	30 (0.226)	0.701 (0.396–1.240)	0.222
T/C	59 (0.488)	80 (0.541)	1.221 (0.754–1.977)	0.417	57 (0.496)	62 (0.466)	0.901 (0.546–1.487)	0.684
T/T	29 (0.240)	36 (0.243)	1.029 (0.587–1.804)	0.921	24 (0.208)	41 (0.308)	1.649 (0.920–2.954)	0.093
$\chi^2 = 2.552$; $p = 0.110$						$\chi^2 = 2.877$; $p = 0.090$		
C	125 (0.517)	144 (0.486)	0.883 (0.625–1.248)	0.481	125 (0.543)	107 (0.402)	0.729 (0.513–1.036)	0.078
T	117 (0.483)	152 (0.514)	1.132 (0.801–1.601)	0.481	105 (0.457)	123 (0.462)	1.372 ()0.966–1.951	0.078
c. –1849C > A – *IDO1* (rs3824259)								
C/C	32 (0.264)	42 (0.284)	1.112 (0.649–1.908)	0.699	21 (0.183)	37 (0.278)	1.679 (0.913–3.085)	0.095
C/A	55 (0.455)	67 (0.453)	0.978 (0.603–1.586)	0.927	60 (0.522)	64 (0.481)	0.863 (0.523–1.423)	0.563
A/A	34 (0.281)	39 (0.264)	0.924 (0.539–1.585)	0.774	34 (0.296)	32 (0.241)	0.762 (0.433–1.341)	0.346
$\chi^2 = 0.150$ $p = 0.698$						$\chi^2 = 2.844$ $p = 0.092$		
C	119 (0.492)	151 (0.510)	1.070 (0.773–1.481)	0.685	102 (0.443)	121 (0.455)	1.337 (0.934–1.914)	0.112
A	123 (0.508)	145 (0.490)	0.935 (0.675–1.294)	0.685	128 (0.557)	109 (0.410)	0.748 (0.522–1.070)	0.112
c.-1493G > C – *IDO1* (rs10089084)								
G/G	20 (0.165)	26 (0.176)	1.076 (0.568–2.041)	0.822	19 (0.165)	20 (0.150)	0.902 (0.455–1.789)	0.768
G/C	63 (0.521)	71 (0.480)	0.849 (0.525–1.375)	0.504	62 (0.539)	65 (0.489)	0.829 (0.503–1.369)	0.464
C/C	38 (0.314)	51 (0.345)	1.148 (0.688–1.917)	0.596	34 (0.296)	48 (0.361)	1.317 (0.771–2.252)	0.314
$\chi^2 = 0.051$ $p = 0.822$						$\chi^2 = 0.739$; $p = 0.390$		
G	103 (0.426)	123 (0.416)	0.959 (0.677–1.358)	0.812	100 (0.435)	105 (0.395)	0.850 (0.587–1.232)	0.391
C	139 (0.574)	173 (0.584)	1.043 (0.737–1.477)	0.812	130 (0.565)	161 (0.605)	1.176 (0.812–1.704)	0.391

$p < 0.05$ along with corresponding ORs are in bold.

antidepressant therapy (Table 6). Therefore, we divided the patients into two groups – those with the total score of Hamilton Rating Scale for Depression after treatment at the maximum of 7 points (marked as the effectiveness of antidepressant therapy) and those with the total score after treatment above 7 points (marked as an ineffective antidepressant therapy). We observed that the T/T genotype and the T allele of c.975-7T > C – *AADAT*(rs1480544) were related to a low effectiveness of the antidepressant therapy, while the C allele of the same polymorphism was positively correlated with a response to the applied SSRIs treatment. In the remaining cases, no correlation between SNP's occurrence and effectiveness of antidepressant treatment was found. Moreover, we showed some significant differences in the distribution of studied polymorphism genotypes and the percentage of Hamilton Rating Scale for Depression (Fig. 1). We found a difference in the percentage dispersion of Hamilton Rating Scale for Depression between the A/A and G/A, G/A and G/G, A/A and G/G genotypes of the c. *456G > A *KAT1* (rs10988134) polymorphism. Moreover, the disturbances were also observed between the C/C and T/C, T/C and T/T, C/C and T/T genotypes of the c.975-7T > C – *AADAT* (rs1480544) polymorphism.

4. Discussion

Among various hypotheses explaining the pathogenesis of depression, impairments in TRYCATs pathway are now considered the major contributor to the development of DD. Elevated TRYCATs markers, i.e.quinolinic acid and kynurenine, were found in depressed patients and may be associated with some incorrect actions of the pathway enzymes [6,7]. In addition, our recent study demonstrated that SNPs of genes encoding two isoforms of tryptophan hydroxylase – an enzyme involved in the initial and rate-limiting step in the synthesis of serotonin and melatonin – modulated the risk of depression Wigner et al., 2017b. In this paper, we reconfirmed that the TRYCATs pathway may be involved in pathogenesis of depression and we studied the relationship between four SNPs in *KAT1*,*AADAT* and *IDO1* (two polymorphisms) genes and the risk of DD occurrence.

One of such key enzymes in TRYCATs pathway is kynurenine aminotransferase encoded by gene localized in 9q34.11.The enzyme plays many important roles, including, its cysteine conjugating beta-lyase activity, transaminase activity towards many amino acids and is involved in salvaging of α-keto acids derived from essential amino acids [52]. As mentioned in the introduction, KAT catalyzes formation of kynurenic acid, which shows neuroprotective potency [7]. Hence, previous studies showed that the change of KAT level may be associated with neurodegenerative disorders [52]. The patients with Alzheimer's disease, Parkinson's disease, multiple sclerosis and Huntington's disease were characterized by a lower concentration of KAT in the central nervous system, while patients with HIV infection, Down's syndrome, amyotrophic lateral sclerosis, schizophrenia and epilepsy had increased level of the enzyme [52]. Up to date, no evidence has been presented to prove a relationship existing between polymorphisms of *KAT1* and the development of neurodegeneration; however, it was established that the SNP analysed in the study causes a transition in the 3′UTR region which may affect a *KAT1* transcript stability [53], http//:genome.UCSC.edu). Additionally, other studies showed that the SNPs in this region of gene may affect mRNA half-life and degradation and, consequently, may lead to an increase or a decrease of gene expression [54,55]. Accordingly,

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Table 6
The impact of the single-nucleotide polymorphisms of genes encoding enzymes on the effectiveness of depression treatment.

Genotype/Allele	Control (n = 236)		Depression (n = 281)		Crude OR (95% CI)*	p
	Number	Frequency	Number	Frequency		
c.*456G > A – *KAT1* (rs10988134)						
A/A	13	0.081	6	0.083	1.020 (0.372–2.798)	0.970
A/G	53	0.329	25	0.342	1.061 (0.592–1.904)	0.842
G/G	94	0.588	43	0.581	0.941 (0.537–1.648)	0.832
$\chi^2 = 0.032$; $p = 0.859$						
A	79	0.245	37	0.253	1.040 (0.677–1.597)	0.858
G	241	0.753	111	0.750	0.962 (0.626–1.477)	0.858
c.975-7T > C – *AADAT* (rs1480544)						
C/C	38	0.236	12	0.164	0.637 (0.311–1.305)	0.218
T/C	88	0.547	34	0.466	0.723 (0.415–1.259)	0.252
T/T	**34**	**0.213**	**28**	**0.378**	**2.113 (1.154–3.870)**	**0.015**
$\chi^2 = 5.363$; $p = 0.021$						
C	**164**	**0.509**	**58**	**0.397**	**0.618 (0.408–0.934)**	**0.023**
T	**156**	**0.488**	**90**	**0.608**	**1.619 (1.070–2.448)**	**0.023**
c. −1849C > A – *IDO1* (rs3824259)						
C/C	51	0.317	17	0.233	0.655 (0.347–1.237)	0.192
C/A	68	0.425	35	0.473	1.162 (0.667–2.026)	0.596
A/A	41	0.255	22	0.301	1.263 (0.684–2.330)	0.456
$\chi^2 = 1.534$; $p = 0.215$						
C	170	0.531	69	0.466	0.791 (0.545–1.148)	0.217
A	150	0.468	79	0.534	1.264 (0.871–1.834)	0.217
c. −1493G > C – *IDO1* (rs10089084)						
G/G	29	0.180	12	0.164	0.895 (0.428–1.873)	0.769
G/C	77	0.481	34	0.459	0.878 (0.504–1.529)	0.646
C/C	54	0.335	28	0.384	1.233 (0.694–2.189)	0.475
$\chi^2 = 0.416$; $p = 0.519$						
G	135	0.422	58	0.392	0.878 (0.591–1.305)	0.520
C	185	0.578	90	0.608	1.139 (0.767–1.691)	0.520

$p < 0.05$ along with corresponding ORs are in bold.

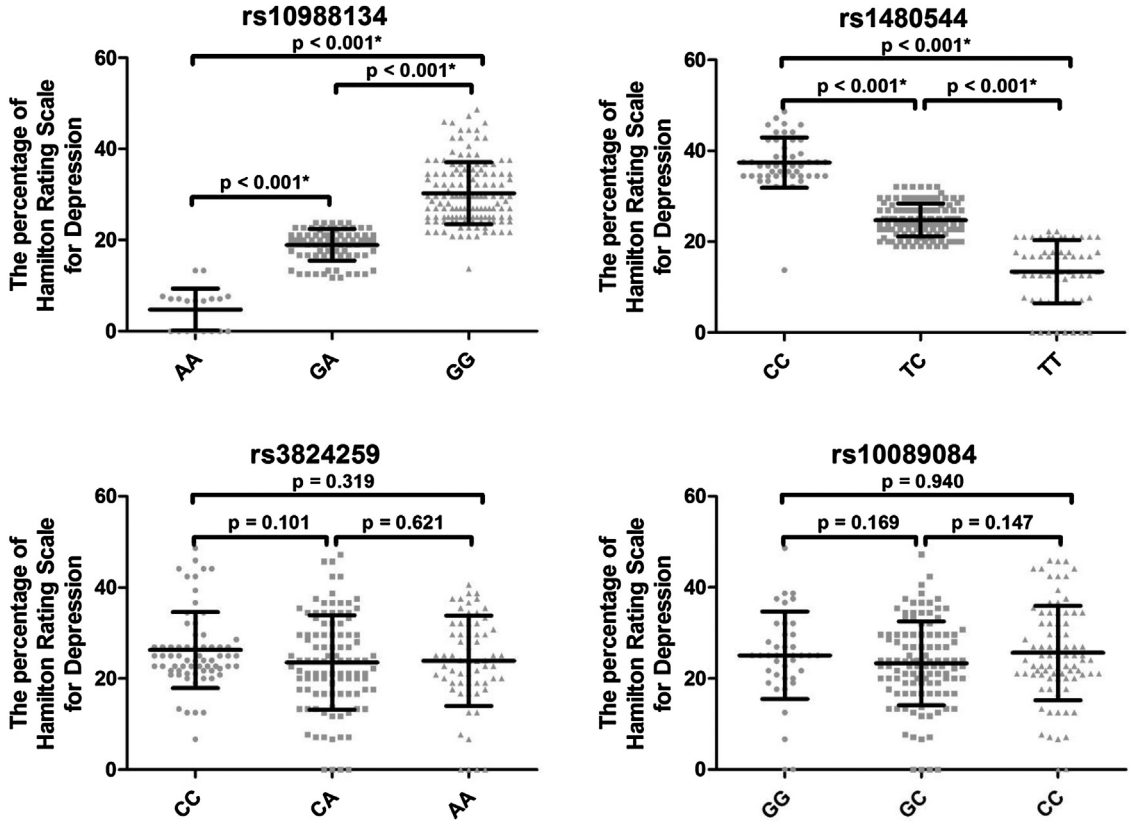

Fig. 1. Distribution of single-nucleotide polymorphisms of genes encoding KAT1, KAT2 and IDO1 and the percentage of the Hamilton Rating Scale for Depression after an antidepressant therapy. Horizontal lines represent the median, while whiskers show the inter-quartile range.

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we were the first to show that the A/A genotype of c.*456G > A – *KAT1* (rs10988134) may increase the risk of depression occurrence ($p < 0.05$)(Table 2). Thus, the A/A genotype may be associated with a decreased concentration or activity of KAT1 and may lead to an increase the level of neurotoxic kynurenine. Interestingly, when we stratified the study group by gender, this association was valid only for the male population ($p < 0.05$) (Table 5.). Although the consequence of this status is unknown, we may speculate that this differences may result from a different enzymes activity or concentration in men and in women group. The next studied polymorphism is located in locus 4q33 encoding AADAT (KAT2). The enzyme demonstrates the activity towards aminoadipate and α-ketoglutarate and catalyzes transamination for a number of amino acids [52]. The c.975-71T > C – *AADAT* (rs1480544) SNP is in a putative exonic splicing silencers (ESSs), thus it may lead to some quantitative changes in the production of canonical mRNAs and peptide [56]. So far, only one study, carried out on the Brazilian population, showed that this SNP may have an impact on the phenotype – the C/T genotype of this SNP affected the host's expression of markers of the immune response to bacterial meningitis [42]. On the other hand, in our study we did not find any significant differences between depressed patients and healthy volunteers (Table 2). However, in gene–gene analyses, we found that the combined genotype of c.975-71T > C – *AADAT* (rs1480544) and c.-1849C > A (rs3824259) of *IDO1* or c.-1493G > C of *IDO1* (rs10089084) may modulate the risk of the depression development ($p < 0.05$) (Table 3). Additionally, we showed that the T/T genotype is associated with poorer outcome of the SSRIs treatment ($p < 0.05$) (Table 6).This discovery can contribute to choosing the right personalized antidepressant treatment.

Lastly, we evaluated distribution of two SNPs encodes indoleamine 2,3-dioxygenase, which catalyzes the first and rate-limiting step in the TRYCATs pathway, leading to initiation of N-formylkynurenine. Both polymorphism present near 5′ (regulatory region) end of *IDO1*–gene located on chromosome 8p11. [57–59]. The previous studies suggested that the SNP in noncoding regions, including introns and regulatory regions, may cause an altered mRNA stability, degradation and expression, resulting in some changes in the activity of the final protein product [60–62]. Despite the potential changes caused by these polymorphisms, we did not detect the link between the SNPs occurrence and the development of depression (Table 2). Similarly, in a study of these polymorphisms frequency in patients with interferon-alpha-related depression in hepatitis C as compared to controls [63] its authors did not find any statistically significant results concerning thesetwo polymorphisms. On the other hand, as mentioned earlier, the combined genotype of either of these SNPs and c.975-71T > C – *AADAT* (rs1480544) may be associated with occurrence of depression ($p < 0.05$) (Table 3).

The present study had some potential limitations. First of all, the sample size was relatively small and consequently of low power, which could lead to both false negative as well as false positive findings. Therefore these results should be interpreted with caution and considered preliminary. Second, the studied population was from Poland only, which reduces the possibility of confounding from ethnicity, so it does not permit any extrapolation of the results to other ethnic groups.

The findings of this work cast a new light on the pathogenesis of depression; however, some additional larger case-control studies on different population groups and functional experiments are necessary before the final resolution about/findings as to the role of the TRYCATs pathway in the development of this disease.

5. Conclusion

In the current work,we showed that the chosen four SNPs of genes involved in tryptophan catabolites pathway may influence the risk of depression occurrence. Therefore, these polymorphisms may be considered as independent depression markers.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eurpsy.2018.05.001.

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